

REMARKS

Claims 1, 11, 36, 42, 43, 82-88, and 90-93 are pending in the instant application.

It is respectfully submitted that the present amendment presents no new issues or new matter and places this case in condition for allowance.

I. The Rejection of Claims 1, 11, 36, 42-43, 82-88, and 90-93 under 35 U.S.C. § 103

Claims 1, 11, 36, 42-43, 82-88, and 90-93 remain rejected under 35 U.S.C. § 103 as being unpatentable over Wilson *et al.* (PNAS 96: 12833-12838, 1999) in view of Cao *et al.* (Mol. Microbiol. 45: 1267-1276, 2002). The Advisory Action stated:

[I]t would have been *prima facie* obvious at the time of applicants' invention to apply the *Bacillus subtilis* strain of Cao *et al.*, to Wilson *et al.*, method for determining the mode of action of an antimicrobial compound in order to provide obtain antimicrobial mode of action results for *B. subtilis* which is known to be resistant to known antimicrobial drugs. Furthermore, one of ordinary skill in the art would have a reasonable expectation of success by exchanging one gram-positive bacterium for another gram-positive bacteria because both bacteria are known in the art to have analyzed on DNA microarrays wherein the hybridization complexes detected in the presence of subinhibitory amounts of antimicrobial compounds.

This rejection is respectfully traversed for the reasons of record and further for the reasons stated below.

The Examiner has the initial burden of establishing a *prima facie* case of obviousness. A finding of obviousness under 35 U.S.C. § 103 requires a determination of the scope and content of the prior art, the differences between the claimed invention and the prior art, the level of ordinary skill in the art, and whether the differences are such that the *claimed subject matter as a whole* would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. John Deere*, 383 U.S. 1 (1966).

Wilson *et al.* disclose exploring drug-induced alterations in gene expression in *Mycobacterium tuberculosis* by microarray hybridization.

Cao *et al.* disclose antibiotics that inhibit cell wall biosynthesis induce expression of the *Bacillus subtilis* σ^W and σ^M regulons.

Applicants submit that Wilson *et al.* and/or Cao *et al.* do not teach or suggest the instant invention. Wilson *et al.* teach the use of DNA microarrays to characterize the global transcriptional response of *Mycobacterium tuberculosis* to isoniazid (INH) at concentrations of 0.2 μ g or 1 μ g of INH per ml, which are above the minimum inhibitory concentration of INH, *i.e.*, 0.02 μ g of INH per ml. Cao *et al.* teach the use of DNA microarrays to

characterize the global transcriptional response of *Bacillus subtilis* to vancomycin at concentrations 10X the minimum inhibitory concentration.

The Office relies on *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) and argues that "no more than routine skill is involved in adjusting the concentration of the claimed process to suit a particular starting material in order to achieve the results taught in the prior art", "[u]sing subinhibitory amounts is not beyond the skill in the art and the resulting invention would have been obvious because a person of ordinary skill has good reason to pursue the known options within his or her technical grasp", and "differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art" on the ground that "where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation."

Applicants disagree with the Office's assertion and submit that the Office's reliance on *In re Aller* is misplaced. *In re Aller* held that "it's obvious to routinely experiment and optimize" according to the facts of *In re Aller*. The facts are very specific in *In re Aller*. *In re Aller* did not hold that "it's obvious to routinely experiment and optimize" if the facts of the application being examined are distinguishable from the facts of *In re Aller*.

The facts in *In re Aller* involve treatment of isopropyl benzene hydroperoxide (or similar organic peroxides) with sulphuric acid, wherein the hydroperoxide is decomposed into phenol and acetone (or other ketones). The process was identical with that of the prior art, except that the claims specified lower temperatures and higher sulphuric acid concentrations than shown in the prior art. The *In re Aller* court stated:

In analyzing these improved results, one is not struck by any difference in *kind* attributable to appellants' process — logically the improvements could flow equally well from changes in *degree* resulting from routine variation in temperature or acid concentration. At the least efficient conditions reported by appellants, the improvement is but a few percentage points different from the results reported by the reference. At the most efficient conditions, the improvement is still within the range of variation one might expect to result from changes in reaction conditions. There is no temperature range or acid concentration range that can really be termed "critical." As far as is shown, temperatures between 80° and 100°C., and acid concentrations between 10% and 25%, could result in increasingly greater efficiency, somewhat more than Hock and Lang, somewhat less than appellants. Appellants have not shown anything "critical" about their process, unless lower temperatures and higher acidity generally are critical.

Consequently, the claimed process in *In re Aller* resulted from experimentally varying the different factors of the prior art process to optimize the reaction and there was no

evidence to indicate that the reported increase in yields was a difference in kind and not of degree.

In the instant application, the facts are different. Applicants have not optimized the minimum inhibitory range of an antimicrobial compound. Wilson *et al.* teach the use of isoniazid (INH) at concentrations of 0.2 µg or 1 µg of INH per ml, which are above the minimum inhibitory concentration of INH. Cao *et al.* teach the use of vancomycin at concentrations 10X the minimum inhibitory concentration. Wilson *et al.* in view of Cao *et al.* teach or suggest the use of microarray hybridization for determining gene expression in response to antimicrobial compound concentrations above their minimum inhibitory concentration of INH. One skilled in the art would recognize that optimization of the inhibitory range of an antimicrobial compound would involve optimal concentrations for inhibiting cell growth, not sub-inhibitory concentrations where there is no or little inhibition of cellular growth. Applicants used sub-inhibitory concentrations where there was no or little inhibition of cellular growth. Consequently, the facts of Applicants' invention are distinguishable over the facts of *In re Aller*. Applicants submit that *In re Aller* is not relevant to the instant application.

Applicants also submit that Wilson *et al.* in view of Cao *et al.* implicitly teach away from using sub-inhibitory amounts of an antimicrobial compound. One of ordinary skill in the art would not be motivated by the cited references to use sub-inhibitory amounts of an antimicrobial compound.

Applicants further submit that the claimed methods produce unexpected results in utilizing sub-inhibitory amounts of an antimicrobial compound. Applicants have shown that the use of sub-inhibitory amounts of an antimicrobial compound result in the ability to more readily identify primary effects of the antimicrobial compound on genes of a bacterial cell and reduce secondary effects on other genes that can result from using high inhibitor concentrations of the compound. The use of sub-inhibitory concentrations consequently slows the action of the compounds, and limits the expression of genes that are correlated to secondary effects, allowing a predominance of expressed nucleic acids that correlate with the activity of the antimicrobial compound, which is related directly, and primarily, with its mode of action on the cell. In contrast, gene expression responses to concentrations of an inhibitor above its minimum inhibitory concentration cause a broader effect on cellular processes by the inhibition of secondary targets within the cell, as well as by downstream effects that result from inhibition of the primary target, thereby giving much more complex response patterns. Applicants' submit that their results exhibit a superior advantage that a person skilled in the art would have found surprising and unexpected.

For the foregoing reasons, Applicants submit that the claims overcome the rejections under 35 U.S.C. § 103 and respectfully request reconsideration and withdrawal of the rejections.

II. Conclusion

In view of the above, it is respectfully submitted that all claims are in condition for allowance. Early action to that end is respectfully requested. The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment or application.

Respectfully submitted,

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